

Serial No. 09/749,637

Amendment dated September 9, 2003

Reply to Office Action mailed 4 August 2003

*AMENDMENTS TO THE SPECIFICATION*

Please replace the paragraph at page 1, line 22 - page 2, line 2 with the following amended paragraph:

Conus is a genus of predatory marine gastropods (snails) which envenomate their prey. Venomous cone snails use a highly developed apparatus to deliver their cocktail of toxic conotoxins into their prey. In fish-eating species such as *Conus magus* the cone detects the presence of the fish using chemosensors in its siphon. When close enough the cone extends its proboscis and impales the fish with a hollow harpoon-like tooth containing venom. This immobilizes the fish and enables the cone snail to wind it into its mouth via the tooth held at the end of its proboscis. ~~For general information on Conus and their venom see the web address grimwade.biochem.unimelb.edu.au/cone/referenc.html~~. Prey capture is accomplished through a sophisticated arsenal of peptides which target specific ion channel and receptor subtypes. Each *Conus* species venom appears to contain a unique set of 50-200 peptides. The composition of the venom differs greatly between species and between individual snails within each species, each optimally evolved to paralyze its prey. The active components of the venom are small peptide toxins, typically 10-30 amino acid residues in length and are typically highly constrained peptides due to their high density of disulphide bonds.

Please replace the paragraph at page 2, lines 3-18 with the following amended paragraph:

The venoms consist of a large number of different peptide components that when separated exhibit a range of biological activities: when injected into mice they elicit a range of physiological responses from shaking to depression. The paralytic components of the venom that have been the focus of recent investigation are the  $\alpha$ -,  $\omega$ - and  $\mu$ -conotoxins. All of these conotoxins act by preventing neuronal communication, but each targets a different aspect of the

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process to achieve this. The  $\alpha$ -conotoxins target nicotinic ligand gated channels, the  $\mu$ -conotoxins target the voltage-gated sodium channels and the  $\omega$ -conotoxins target the voltage-gated calcium channels (Olivera et al., 1985; Olivera et al., 1990). For example a linkage has been established between  $\alpha$ -,  $\alpha$ A- &  $\psi$ -conotoxins and the nicotinic ligand-gated ion channel;  $\omega$ -conotoxins and the voltage-gated calcium channel;  $\mu$ -conotoxins and the voltage-gated sodium channel;  $\delta$ -conotoxins and the voltage-gated sodium channel;  $\kappa$ -conotoxins and the voltage-gated potassium channel; conantokins and the ligand-gated glutamate (NMDA) channel. Five  $\delta$ -conotoxins have been described: GmVIA (U.S. Patent No. 5,719,264); PVIA (U.S. Patent No. 5,739,276); TxVIA (Hillyard et al., 1989; Fainzilber et al., 1991); TxVIB (Fainzilber et al., 1991); NgVIA (Fainzilber et al., 1995); and TxIIA (Nakamura et al., 1996). ~~For a partial list of Conus peptides and their amino acid sequences see the website address~~  
<http://pir.georgetown.edu>.

Please replace the paragraph at page 4, lines 9-24 with the following amended paragraph:

Examples of synthetic aromatic amino acid include, but are not limited to, nitro-Phe, 4-substituted-Phe wherein the substituent is C<sub>1</sub>-C<sub>3</sub> alkyl, carboxyl, hydroxymethyl, sulphomethyl, halo, phenyl, -CHO, -CN, -SO<sub>3</sub>H and -NHAc. Examples of synthetic hydroxy containing amino acid, include, but are not limited to, such as 4-hydroxymethyl-Phe, 4-hydroxyphenyl-Gly, 2,6-dimethyl-Tyr and 5-amino-Tyr. Examples of synthetic basic amino acids include, but are not limited to, N-1-(2-pyrazolinyl)-Arg, 2-(4-piperidinyl)-Gly, 2-(4-piperidinyl)-Ala, 2-[3-(2S)pyrrolidininyl]-Gly and 2-[3-(2S)pyrrolidininyl]-Ala. These and other synthetic basic amino acids, synthetic hydroxy containing amino acids or synthetic aromatic amino acids are described in Building Block Index, Version 3.0 (1999 Catalog, pages 4-47 for hydroxy containing amino

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acids and aromatic amino acids and pages 66-87 for basic amino acids; ~~see also~~ <http://www.amino-acids.com>), incorporated herein by reference, by and available from RSP Amino Acid Analogues, Inc., Worcester, MA. The residues containing protecting groups are deprotected using conventional techniques. Examples of synthetic acid amino acids include those derivatives bearing acidic functionality, including carboxyl, phosphate, sulfonate and synthetic tetrazolyl derivatives such as described by Ornstein et al. (1993) and in U.S. Patent No. 5,331,001, each incorporated herein by reference.